DATA EVALUATION RECORD

Slug & Snail Killer, Sodium Ferric hydroxyl Ethylenediaminetetraacetate (EDTA)

STUDY TYPES:
Dietary Risk Assessment for Slug and Snail Killer, File Symbol No. 42697-AR.

MRID 473029-02

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DATA EVALUATION RECORD

EPA Secondary Reviewer:

STUDY TYPE:	Dietary Risk Assessment for Slug and Snail Killer
MRID NOS:	473029-02
DP BARCODE NO:	DP 348433
CASE NO:	Not reported
DECISION NO:	352633
TEST MATERIAL:	Sodium ferric etthylenediaminetetraacetate (6%)
PROJECT NO:	Not reported
SPONSOR:	Woodstream Corporation
TESTING FACILITY:	N/A (Studies from the published literature).
SUBMITTER REPRESENTATIVE:	Eliot Harrison, Agent for woodstream
FILE SYMBOL:	42697-AR
STUDY COMPLETED:	December 9, 2007
GOOD LABORATORY PRACTICE:	Not GLP Compliant, descriptive information
CONCLUSION:	There is adequate information available to support the requested exemption from the requirement of a tolerance for Sodium Ferric (III) EDTA complex on home gardens when applied as specified on product label to control slug and snail pests.
CLASSIFICATION:	Acceptable

Background

Woodstream is pursuing registration of a new molluscicide product , Slug and Snail Killer (EPA Reg. No. 42697-AR). The product is a pellet that contains a new active ingredient, 6% w/w Sodium Ferric (III) EDTA complex. The complex is comprised of sodium Ferric (III), Hydroxy EDTA (monomer and dimmer), sodium Ferric (III) Dihydroxy EDTA and Sodium Ferric (II) EDTA. The registrant is submitting a dietary risk assessment that is equivalent to a tolerance or tolerance exemption petition for use of Slug and Snail Killer on vegetable home gardens. Applications of this product are restricted to soil-directed applications around and adjacent to plants. Use instructions for vegetables, berries, grapes vines, and fruit trees are as follows: "Application rates: 0.5 to 1.0 lb per 1,700 sq. ft. Scatter the bait around the perimeter of the vegetable plot as a protective barrier or apply directly to the soil around the base of the plant and between the rows. Do not broadcast the entire area. Reapply every 14 days while pest infestation persists." No application will be made on or over plants. Even if a few pellets inadvertently contact fruits and vegetables, the pellets are unlikely to adhere to the skin of these crops.

Dietary residues

Except for hydroxyl ion, the dietary residues from Slug and Snail Killer are the same as those resulting from dissociation of free iron, EDTA, and hydroxyl ions from Sodium Ferric (III) EDTA used as micronutrient fertilizer treatments for iron-deficient soil amends.

Chelated iron micronutirent fertilizers contain higher concentrations of iron (15%) and higher application rates than Slug and Snail Killer (0.5 to 1.0 lb per 1,700 sq. ft. applied directly to the soil around the base of plants and between rows). Foliar spray applications of chelated iron microfertilizer on fruit crops range from 1to 3 lb per 100 gallon, and band or sidedress soil applications range from half to 1 lb per 100 ft of row. For vegetables, applications range from 1 ½ to 5 lb per acre, depending on the type of vegetable and application method, water or band, respectively.

Dietary Assessment

Sodium ferric (III) EDTA complex is very similar to FeNaEDTA, which has been classified as "Not a biochemical, but eligible for a reduced data set" per EPA' letter received 3-16-2001". The only difference is that the sodium Ferric (III) complex includes some hydroxylated species, identified as sodium ferric III hydroxy EDTA (monomer and dimmer) and sodium ferric Dihydroxy EDTA. This complex dissociates in soil and in the human gut to free iron, EDTA salt and hydroxyl ion. These hydroxyl ions can be considered insignificant from a dietary risk perspective.

Hazard Profile

Ethylenediaminetetraacetic acid (EDTA) is a chelator capable of combining stoichiometrically with virtually every metal in the periodic table (Chaberck and Martell, 1959). The effectiveness of EDTA as a chelate for a particular metal ion is given by its stability constant with the metal ion. Chelation potential is affected by pH, the molar ratio of chelate to metal ion, and the presence of competing metal ions capable of forming complexes with EDTA (Plumb et al. 1950; Martell, 1960; Hart, 1984). The stability constants for different metal-EDTA complexes vary considerably and any metal which is capable of forming a strong complex with EDTA will at least partially displace another metal. Ferric ion has the highest stability constant (log k of 25.1), and an optimum pH = 1 for chelate formation. When ingested with food, the ferric ion is bound to the moiety in the stomach, but exchanged for other metals takes place in the duodenum as the pH rises. Similarly, when sodium EDTA or sodium calcium EDTA are consumed with foods, the sodium and calcium ions are predominantly exchanged for ferric ions in the stomach, which is in turn exchanged for sodium and calcium ions in the duodenum. As stated earlier, the extend to which complex forms is dependent on pH, concentration of competing metals, as well as competing ligands. In summary, when ferric EDTA is ingested, the chelate holds the iron in the stomach until pH rises in the upper small intestine. As pH rises, the strength of the complex progressively diminishes allowing exchange with other metals and iron for absorption. Iron dissociates from the EDTA moiety and is released in the duodenum prior to absorption. Only a very small fraction of the NaFeEDTA complex (less than 1%) is absorbed intact. Intact EDTA metal complexes are rapidly excreted. They don't accumulate or undergo biotransformaition.

EDTA may interfere with absorption or retention of essential minerals in humans only when it is present in large amounts; but moderate doses are innocuous. The upper limits of iron established by the Institute of Medicine (IOM) are is 45 mg/p/d for adults and adolescents (14 and 18 years

of age); 40 mg/p/d for infants up to 1 year of age, and children between 1 and 13 years of age. IOM's derivation of UL for the general population does not consider individuals with iron loading abnormalities or with heredity hemochromatosis and liver disease; these populations are exceptionally sensitive to the effects of iron overload. Acute iron toxicity in humans may occur by ingestion of as little as 25 mg/kg bw/d of iron, with clinically significant iron poisoning occurring at doses of 60 mg/kg/bw/d of iron.

The acceptable daily intake (ADI) for EDTA established by Joint WHO/FAO Expert Committee on Food Additives (JECFA) is 2.5 mg/kg bw/d. The recommended daily allowance (RDA) for iron varies with age and gender from 6 mg/p/d for adult men between 19 and 70 years of age to 18 mg/p/d of iron for menstruating women between 19 and 50 years of age. The RDA has not been set for infants 0 to 6 months of age.

Results from acute toxicity studies with disodium EDTA are summarized in the following table:

Table 1. Results from acute toxicity studies with disodium EDTA.

Animal	**Route**	**Disodium EDTA LD50 (mg/kg bw)**	**References**	**Ca-disodium EDTA LD50**	**References**
rat	oral	2,000 – 2,200	Yang, 1964	10,000 ± 740	Oser et al. 1963
rabbit	oral	2,300	Shibata, 1956	7,000	Oser et al. 1963
Dog	oral	12,000			Oser et al. 1963

In a memorandum from EPA Registration Division, dated January 28, 2004, the Agency limits the percent of EDTA or any EDTA salt in a formulated pesticide product to 5% by weight. Based on the Agency's assessment of available information on the use, physical/chemical properties, toxicological effects, and exposure profile of EDTA and EDTA salts, EPA concludes that there is reasonable certainty of no harm to the general population and to infants and children from aggregated exposure of EDTA and its various salts from their uses as ingredients in pesticide products. This assessment is based on reviews performed by federal Drug Administration (FDA), Food and Agriculture Organization of the World Health Organization (FAO/WHO), and the Cosmetic Integrated review (CIR).

The following toxicological data were obtained from published reports by peer-reviewed committees such as the Joint FAO/WHO Expert Committee on Food Additives (JECFA), Scientific Committee on Toxicity, Ecotoxicity, and the Environment (SCTEE), Cosmetic

Ingredient Review (CIR), published studies in peer-reviewed journals, as well as from NIOSH, and other data base available such as TOXNET and SIRI. In general, EDTA and its salts are sequestrants which have the ability to chelate metals. EDTA is not totally absorbed when ingested. Elimination occurs mainly by the kidneys (95%) with some 5% via the bile. EDTA

and its salts are mild skin irritants but considered severe eye irritants. The main risk in the human body occurs when EDTA uptakes trace metals used and required by the body. This can lead to developmental problems when the body is not properly supplemented with necessary trace metals. The teratogenic effects reported in Kimmel (1977) study are likely to be the result of zinc deficiency. A more recent study by Schardein et al. (1981) indicated no teratogenic effects in rodents at doses up to 1000mg/kg. Maximum human consumption of EDTA and its salts in foods has been reported in the order of 0.4 mg/kg/day (Schardein et al. 1981).
The CSTEE (2003) reviewed a study by the National Cancer Institute (NCI, 1977), and concluded that there is no concern for EDTA regarding carciogenecity.
Mutagenicity studies results were negative for EDTA and its salts except for few positive tests. Genotoxicity studies for EDTA and its salts were mixed positive and negative results, depending on assay type and cell type (CCRIS 2003 and Genetox 2003).
The SAR assessment of 15 EDTA salts, including ferric EDTA and sodium ferric EDTA indicate no absorption through the skin but expected good absorption through the lungs and gastrointestinal tract.
The use of EDTA and its salts in pesticides are not likely to exceed levels currently consumed in foods and cosmetics.

EPA does not have, at this time, available data to determine whether EDTA and its salts have a common mechanism of toxicity with other substances.

Environmental fate/ Ecotoxicity / Drinking water considerations

EDTA is a strong organic acid. When released to soil or water, it is slow to degrade, with aerobic biodegradation (mineralization) being the dominant mechanism. When released to water, EDTA is expected to form soluble complexes with trace metals and alkaline earth metals. It is not expected to sorb appreciably to sediments or suspended solids in water. In soils, EDTA is mobile and expected to complex trace metals and alkaline earth metals, thereby increasing metal solubility. EDTA predominates as ferric (III) chelate in acidic soils and as Ca chelate in alkaline soils. Although EDTA is slow to degrade under typical environmental conditions, based on its intrinsic physicochemical properties (ionic nature and water solubility), it is not expected to bioconcentrate or volatilize from soil or water. The rate of biodegradation of EDTA in soils is reported to vary among soils with rates depending upon environmental factors such as pH, temperature, soil classification, organic matter, and type microbe populations. EDTA and its chelates are expected to leach readily through soil. In water, EDTA may react with photochemically generated hydroxyl radicals (half-life of approximately 230 days or 8 months). The following photodegradation products have been identified: CO, formaldehyde, ED3A, N,N-EDDA, IDA, EDMA, and glycine. When released to the atmosphere, EDTA sorbs to particulate matter and undergoes photolyzation.

Ecotoxicity and Ecological Risk Characterization

Toxicity of EDTA ranges from practically non-toxic to moderately toxic on an acute basis depending on the salt. Algae and invertebrates are the most sensitive species for acute and chronic endpoints depending on the EDTA compound. The following table lists the estimated toxicity for several compounds of EDTA:

Table 2. Ecotoxicity of Ferric EDTA and ferric (III) EDTA salts.

Organisms	Toxicity level
Fish	96-h LC_{50} = 430 mg/L
Daphnia	48-h LC_{50} = 100 mg/L
Green algae	96-h EC_{50} = 3.00 mg/L
Fish	Chronic = 10 mg/L
Daphnia	Chronic = 23 mg/L
Algae	Chronic = 0.88 mg/L

Based on the environmental fate profile of EDTA and its salts, exposures from label uses are unlikely to reach concentrations necessary to elicit effects in most aquatic organisms. Laboratory rat data used as surrogate for terrestrial mammals and birds show that EDTA and its salts are not very toxic and adverse effects from label uses are not expected.

References:

Laan R.G. W., Verbug T., Wolterbeek H.Th., de Goeij J.M. 2004. Photodegradation of Iron(III)-EDTA: Iron speciation and domino effects on cobalt availability. Environ. Chem. I: 107-115.

EPA Memorandum on Metaldehyde Alternative Assessment by BEAD Product Review Panel dated June 28, 2006 (with references therein).

Sodium Iron EDTA Hazard Assessment by WHO Food Additives Series 32 (with references therein).

FDA Response Letter to GRAS Notice No. GRN 000152

EPA Tolerance Reassessment Decisions Completed by the lower Toxicity Chemical Focus Group dated January 28, 2004 (references therein).

EPA Reregistration Eligibility Document (RED) Iron Salts List D CASE 4058 dated February 1993.

Iron (Ferric Phosphate (034903) Technical Document date issued October,1998. Last updated October 22, 2007.